Bovine Spongiform Encephalopathy: History, Concerns and Actions of the US Food and Drug Administration regarding Vaccines

Joint Meeting of the FDA Transmissible Spongiform Encephalopathies and the Vaccines and Related Biological Products Advisory Committees

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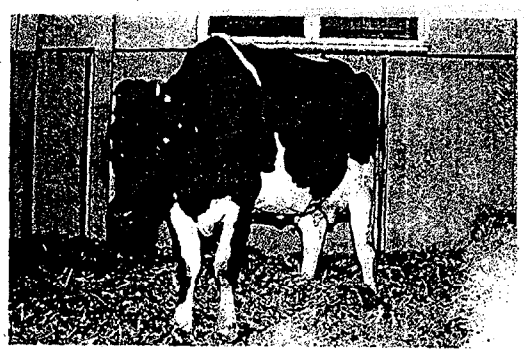
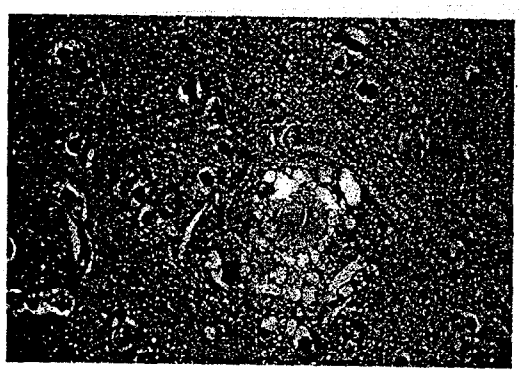
BSE Risk and Vaccines

- Vaccine components of current concern
- FDA and CBER BSE regulatory history
- USDA relevant BSE rules and policies
- General elements of BSE risk assessment
  - Sources of bovine material
    - Temporal BSE risk
    - Geographic BSE risk
    - Tissue BSE risk
  - Manufacturing process
  - End use
- Factors potentially mitigating risk





Sporadic and New-variant CJD

(modified from Will & al. Lancet 1996;347:921)

- Sporadic CJD
  - Mean age ~65 yr
  - Mean duration ~ 4 mo
  - Presentation: confusion, sometimes ataxia
  - EEG: periodic suppression-burst, slowing
  - PRNP codon 129 met/met ~80% (vs ~50% gen'l pop.)
  - Amyloid plaques in ~15% of patients (rarely "florid")
  - PrP^{Sc} size, glycoform abundance: not BSE type
  - sCJD lesion profile in mice
  - sCJD-like properties in bovinized-PrP Tg mice
- New-variant CJD
  - Mean age ~29yr (13 to 52)
  - Mean duration ~ 12 mo
  - Presentation: abnormal behavior, dysesthesia
  - EEG: slowing without periodic suppression-burst
  - PRNP codon 129 met/met 100%
  - Amyloid florid plaques in 100%, of patients
  - PrP^{Sc} size, glycoform abundance: BSE type
  - BSE lesion profile in mice
  - BSE-like properties in bovinized-PrP Tg mice

Bovine Materials from BSE Countries of Concern in Manufacture of CBER-Regulated Vaccines

Bovine Material	EU Risk Category of BSE Country
Serum	IV
Gelatin Derivative	II, III
Pancreatic Extract	III
Skeletal Muscle Broth	III

FDA Regulation and Polices to Increase Safety of Bovine-derived Materials with Regard to BSE

- FDA regulations (21 CFR 610.18 et seq.) require that "Cultures used in the manufacture of [biological] products ... shall be ... free ... from extraneous organisms [and] ... tested for the presence of detectable microbial agents [as] ... necessary to assure the safety, purity and potency of a product ..."
- May 1991: CBER letter to mfg of biological products, expressed concern about TSEs and requested information on sources of ovine and bovine materials including, sera, enzymes, etc.

FDA Polices to Increase Safety of Bovine-derived Materials with Regard to BSE

- May 1993: CBER revised Points to Consider (PTC) in the Characterization of Cell Lines Used to Produce Biologicals, recommending that "... serum or additives [in] ... culture ... medium should be free from contaminants and adventitious agents, such as the agent responsible for the production of Bovine Spongiform Encephalopathy."
- Jul 1993: CBER letter asked mfg to review PTC.
- Dec 1993: FDA requested that most bovine-derived materials from animals born or living in BSE countries not be used to manufacture FDA-regulated products intended for humans. Letters noted that USDA maintains the list of BSE countries.

FDA Polices to Increase Safety of Bovine-derived Materials with Regard to BSE

- May 1996 (following first reports of vCJD): FDA sent letters to manufacturers of regulated drugs, biologics and devices strongly recommending that they " ... take whatever steps are necessary to assure [them]selves and the public that, in the manufacture of FDA-regulated products intended for administration to humans, [they are] not using materials that have come from cattle born,raised, or slaughtered in countries where BSE is known to exist ... [t]he list [of which] ... is maintained by the ... USDA ..."

FDA Polices to Increase Safety of Bovine-derived Materials with Regard to BSE

- 19 April 2000: CBER again sent letters to manufacturers of biological products reminding them of BSE policies:

  " ...[A]ssure that materials from all species of ruminant animals born, raised or slaughtered where BSE is known to exist or where the USDA has been unable to assure FDA that BSE does not exist, are not used in the manufacture of FDA-regulated products intended for administration to humans."

19 April 2000: CBER Letter to Manufacturers of Biological Products (continued)

- " The Agency has previously recommended that manufacturers take the following steps to prevent this occurrence:"
  - Identify all ruminant-derived materials used; include all cell banks and all materials used in fermentation, harvesting, purification and formulation of the products.
  - Document country of origin and obtain certification of veterinary regulatory inspection of slaughter.
  - Maintain traceable records.
  - USDA (APHIS) maintains the list of BSE countries and BSE-status-unknown countries.

Safety of Gelatin and Gelatin By-products Derived from Potentially TSE-agent Contaminated Sources

- July 1994: FDA did not object to use of bovine-derived materials from BSE countries in manufacture of pharmaceutical-grade gelatin; FDA considered it prudent to obtain all raw materials from non-BSE countries.

  The exemption of gelatin from sourcing recommendations reflected an explicit conclusion by FDA that "... available evidence does not suggest transmission ..." of TSE by gelatin, based on an assessment that manufacturing conditions for gelatin were likely to inactivate the infectious agent.
- FDA implicitly relied on a "species barrier" between cows and humans thought to protect humans from infection with BSE agent. (After more than 60 years of research, there is no evidence that sheep scrapie agent has infected humans.)

Reasons that FDA Reconsidered the Safety of Gelatin from BSE Countries (1996)

- New-variant CJD was recognized in UK and France.
- Experimental data failed to show that processing of gelatin removed all TSE infectivity from contaminated raw materials.
- FDA learned that some source materials for imported gelatin might contain neural tissues of cattle from BSE countries.

Current FDA BSE Gelatin Policies

FDA Guidance
(Sept 1997; rev Dec 1997)

- No gelatin from BSE countries in injectable, implantable or ophthalmic products
- Acceptable for oral, topical use with additional precautions
  - Healthy source cattle
  - BSE-free herds
  - Head, spines and spinal cord should be removed immediately after slaughter

TSEAC Advice
(Apr 1998)

- Agreed with FDA guidance
  (Suggested that spinal column can be safely removed from carcass later.)

Current FDA BSE Policies on Gelatin, Tallow and Tallow Derivatives: Summary

Route	Gelatin	Tallow	Tallow Derivatives
Injectable &c	BSE-Free†	Not Used	BSE-Free#
Oral (food, pharm)	BSE+precautions§	BSE-Free	BSE-Free#
Topical	BSE+precautions§	BSE-Free	BSE-Free#

&c Implantable and ophthalmic
† TSEAC advice was not solicited by FDA.
# TSEAC advised BSE country acceptable if mfg process adequate, validated.
§ TSEAC advised slightly modified precaution.

USDA Regulations Concerning BSE and the Safety of Bovine Gelatin and Serum

- Dec 1991: Bovine gelatin from BSE countries is "...not to come in contact with ruminants...[and importers of gelatin from BSE countries must obtain veterinary permits] ...for Importation and Transportation of Controlled Materials and Organisms and Vectors..." FR 1991;56:63865
- Sept 1993: "...[G]elatin derived from ruminants [from BSE countries] poses a risk of spreading BSE [to ruminants]." FR 1993;58:50250
- USDA has prohibited importation into the USA of bovine serum from countries with BSE for purposes other than scientific, educational and research--for which a permit is required. 9 CFR 95.4

USDA APHIS Requirements for Import of Ruminant Serum (RS)
(Veterinary Services Notice 98-05/19 Mar 1998)

- "[A]pplies to the importation of all categories of RS including fetal calf serum ... "
- "Because of the potential livestock disease risks involved ... [t]he importation of RS is prohibited from all countries not recognized by USDA as being free of foot-and-mouth disease (FMD) and bovine spongiform encephalopathy (BSE)."

USDA APHIS Regulation Concerning Importation of Materials from Ruminants that Have Been in Regions in Which BSE Exists
(9 CFR 95.4)

- "...[T]he importation of bone meal, blood meal, meat meal or tankage, offal, fat, and glands, from ruminants that have been in any region listed in [9CFR]94.18 [the USDA list of countries where BSE either exists or '...with import requirements less restrictive than those...acceptable for import into the United States and/or...inadequate surveillance...' essentially comprising all other European countries] is prohibited."
- "[T]he importation of serum from ruminants in any region listed in [9 CFR] 94.18...is prohibited..."

USDA APHIS Regulation Concerning Import of Materials from Ruminants that Have Been in Regions in Which BSE Exists (9 CFR 95.4)

"[T]he importation of serum from ruminants in any region listed in [9 CFR] 94.18 ... is prohibited, except that serum from ruminants may be imported for scientific, educational, or research purposes if the Administrator [of APHIS Veterinary Services] determines that the importation can be made under conditions that will prevent the introduction of bovine spongiform encephalopathy into the United States...accompanied by a permit issued by [APHIS] ...". [United States Veterinary Permit for Importation and Transportation of Controlled Materials and Organisms and Vectors]

USDA Regulations and Policies Concerning Importation of Bovine Materials:

The United States Veterinary Permit for Importation and Transportation of Controlled Materials and Organisms and Vectors

The permit "DOES NOT authorize direct or indirect exposure of or inoculation into laboratory or domestic animals, including poultry, cattle, sheep, swine, horses, etc. Work shall be limited to IN VITRO uses only."

USDA (APHIS) Interim Regulation Regarding BSE and European Ruminant Products

- Announcement Dec 1997 (published 6 Jan 1998 FR 1998;63:406-408)

  Pending clarification of the status of European countries, as a preventive step, the USDA prohibited importation of all live ruminants and most ruminant products (excluding gelatin [for human consumption], milk and milk products) from all countries of Europe due to potential risk of BSE.

Appearance of BSE Cases in Native Cattle

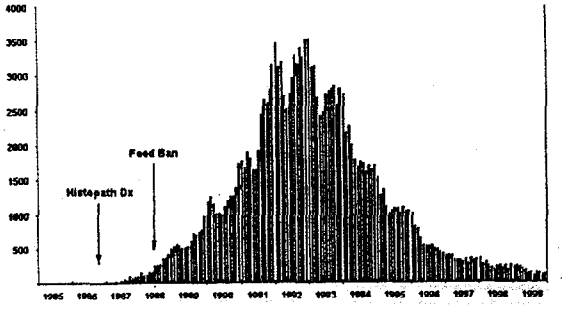
Country	Earliest Birth Yr	1st Yr Dx	Peak Yr Dx	Native Cases to Date	Native Cases 1999
UK[a]	1973-4	1986	1992-3	178,459	2,280
Ireland	1981	1989	1999[b]	469	91
France	1981	1991	1999	100	30
Portugal	1984	1994	1999	371	170
Switzerland	1984	1990	1995	354	50[c]
Belgium	1993	1997	1998	14	4
Netherlands	1993	1997	1999	6	2
Denmark	1996	2000	2000	1	1
Luxembourg	?	1997	1997	1	0
Liechtenstein	?	1998	1998	2	0

a UK data are from MAFF's BSE Enforcement Bulletin 2000;(46):2.
(All other data are from the OIE WebSite <www.oie.int/status/a_bse.htm>)
b Countries with "peak" year 1999 may not have peaked yet.
c Switzerland began active surveillance of clinically healthy slaughter cattle in 1999.

BSE Countries by Probable 1st Appearance in Native Cattle (EU SSC estimates)

- ? Late 1970's
  - UK
- Early-Mid 1980's
  - Ireland
  - France
  - Portugal
  - Switzerland
- Mid 1990's
  - Belgium
  - Netherlands
  - Denmark
  - [? Liechtenstein, ? Luxembourg]
- Not Confirmed but Probably Present
  - Germany
  - Italy
  - Spain

Cases of BSE Registered in GB through 1999 (MAFF)



Geographical Risk of BSE (GBR):
Scientific Steering Committee of the EU/25 May 2000

The GBR is intended to estimate the probability at a given time that cattle in a country are infected with the BSE agent and the probable incidence of BSE in countries where the presence of BSE is confirmed.

GBR of the country of origin is not the only factor affecting the risk that a bovine material is contaminated with BSE agent.

Factors (partial) Considered in EC GBR:
Scientific Steering Committee of the EU/25 May 2000

- Size of national ruminant herd
- Imports of cattle, meat-&-bone meal (MBM)
- Feed and rendering policies
  - Feed bans
  - MBM rendering (?>132 C/20'/3 bar)
- Specified risk materials (SRM) bans
- Culling of ruminants with possible TSE
- TSE surveillance (active or passive)

Ruminant TSE Surveillance Programs

- **Passive surveillance of BSE:** Only suspect animals (neurologically abnormal) are sampled for histopathological and immunodiagnostic confirmation

  UK, Swiss experience: <50% true cases are detected.
- **Active surveillance of BSE:** Both suspect and other cattle >24 mo old are sampled

  Sampling of younger animals does not improve detection.

EU SSC GBR:
Main Elements of Risk

- **Challenge:** Opportunities for BSE agent to enter a national cattle herd
  - External: Imports (especially of UK cattle 1988-93, UK MBM 1986-90)
  - Internal: Recycling of BSE-contaminated MBM from infected cattle
- **Stability:** Effective and prompt removal (by national control activities) of potentially BSE-contaminated materials from contact with cattle
  - *TSE surveillance, culling: elimination of* neurologically abnormal or fallen animals
  - Feed bans: Enforced compliance, reduced cross contamination with other feeds

Geographical Risk of BSE (GBR):
Scientific Steering Committee of the EU 25 May 2000

- "[The EU GBR is intended to] ... overcome the intrinsic limitations of [national BSE] incidence figures alone ... not to qualify the risk with regard to acceptability [which is] ... the responsibility of the risk managers ..."
- "GBR assessments are mainly based on information provided by the assessed countries [plus EC veterinary inspections and UK trade figures] ... Whenever evidence is not convincingly provided, the principle of realistic worst case assumption is applied ..."

EU SSC Estimated Geographic BSE Risk for 25 Responding Countries

- <u>High (Category IV)</u>
  - UK
  - Portugal
- <u>Lower (Category III)</u>

  [Many] Confirmed Cases
  - Ireland
  - France
  - Switzerland
- <u>Lower (Category III)</u>

  [Fewer] Confirmed Cases
  - Netherlands
  - Belgium
  - Luxembourg
  - Denmark
  - [Liechtenstein]
- <u>Lower (Category III)</u>

  Suspected [by SSC] Cases
  - Germany
  - Italy
  - Spain

EU SSC Estimated Geographic BSE Risk for 25 Responding Countries (continued)

- European Countries Provisionally Free of BSE (Category II)
  - Austria
  - Czech Republic
  - Finland
  - Slovak Republic
  - Sweden
- Other Countries Provisionally Free of BSE (Category II)
  - Australia
  - Canada
  - Chile
  - USA

EU SSC Estimated Geographic BSE Risk for 25 Responding Countries (concluded)

- Countries Free of BSE (Category I)
  - Argentina
  - New Zealand
  - Paraguay
  - Norway (EC will review; imported cattle from Denmark.)

Bovine Tissues Known to be Infected with BSE Agent or Banned as Precaution in UK

- Demonstrated to be Infected
  - Brain
  - Trigeminal Ganglia
  - Spinal Cord
  - Dorsal Root Ganglia† (not cauda equina)
  - Eye (retina)
  - Proximal Ileum (exp't'l)
  - Sternal Bone Marrow (?)

  (?) possible artifact

  † prompted deboning of beef in UK (later rescinded)
- Specified Risk Materials Banned in UK (cattle >6mo)
  - Brain
  - Spinal Cord
  - Eye
  - Intestines: duodenum to rectum (any age)
  - Spleen*
  - Tonsils*
  - Thymus* (any age)

  * known infected tissues in sheep and goats with scrapie

BSE Bovine Tissue Risk

(Opinion of the EC SSC on Specified Risk Materials of Small Ruminants, 13-14 Apr 2000 [http://Europa.eu.int/comm/dg24/health/sc/ssc/out78_en.pdf])

- High Infectivity (category 1)
  - Brain
  - Eyes
  - Spinal cord
  - Dorsal root ganglia
  - Dura mater
  - Pituitary
  - Skull
  - Vertebral column
  - Lungs
- Medium Infectivity (category 2)
  - Total intestine (duodenum to rectum)
  - Tonsils
  - Spleen
  - Placenta
  - Uterus
  - Fetal tissue
  - Adrenal
  - CSF
  - Lymph nodes

BSE Bovine Tissue Risk

(Opinion of the EC SSC on Specified Risk Materials of Small Ruminants, 13-14 Apr 2000 [http://Europa.eu.int/comm/dg24/health/sc/ssc/out78_en.pdf])

- Low infectivity (category 3)
  - Liver
  - **Pancreas**
  - Thymus
  - **Bone marrow**
  - **Bones (other)**
  - Nasal mucosa
  - Peripheral nerves
- No detected infectivity (category 4)
  - **Skeletal, heart muscles**
  - Kidney
  - Colostrum and milk
  - Adipose tissues
  - Salivary gland and saliva
  - Mammary gland
  - Ovary, testis, seminal vesicle
  - Cartilage
  - Connective tissue
  - Skin, hair
  - **Blood clot, serum**
  - Bile
  - Urine, feces

Distribution of Infectivity in Tissues of Patients with Spongiform Encephalopathy

(Brown P et al. Ann Neurol 1994;35:513-529)

Tissue	Transmitted/Inoculated
Lung	50% (2/4)
Lymph node	20% (3/15)
Kidney	18% (5/28)
CSF	15% (4/27)
Liver	11% (4/35)
Spleen	10% (3/31)

Precautionary Principle

European Commission COM (2000)1
(European concept--no status in US law)

"Where there is uncertainty as to the existence or extent of risks to human health ... institutions may take protective measures without having to wait until the reality and seriousness of those risks become fully apparent."

[EC Court ruling of 5 May 1998 on EC decision to ban export of UK beef.]

Place of the Precautionary Principle in Decisions about Risks

European Commission COM (2000)1

- Society has the right to establish a level of protection against risk that it deems appropriate.
- Risk must be assessed, managed, and communicated to the public.
- The Precautionary Principle describes an approach to managing a risk that cannot be accurately and confidently assessed.
- Decisions on acceptable levels of risk are political, based both on science and public concern.

Opinion on the Safety of Ruminant Blood with Respect to TSE Risks:

EC Health & Consumer Protection Directorate General
Scientific Steering Committee 13-14 Apr 2000
[http://europa.eu.int/comm/dg24/health/sc/ssc/out74_en.pdf]

"... [T]he data from both experimentally-induced and natural TSE suggest that blood has at least the potential to transmit disease ... There is little doubt that, under certain circumstances, humans or animals could be exposed to the BSE agent by consuming blood products ... Where an element of risk is perceived, this may be reduced or eliminated by (a combination of) various strategies ... Source bovine blood from BSE-free areas or closed herds or other schemes that reduce to a minimum the probability of an animal being infected ..."

Possible Sources of TSE Agent in Bovine Blood

EC Health & Consumer Protection Directorate General
Scientific Steering Committee 13-14 Apr 2000
[http://europa.eu.int/comm/dg24/health/sc/ssc/out74_en.pdf]

- **Intrinsic infectivity**
  (a possible natural part of the TSE disease process)
  - Experimental TSEs in rodents (scrapie, GSS): Infectivity consistently is present in blood late in incubation period.
  - Pathogenesis studies of other TSEs suggest some infectivity in blood.
  - Infectivity in blood may not be"significant"--i.e. usually insufficient in amount to infect except directly into CNS.
- **Extrinsic infectivity**
  (possible contamination of blood with SRM)
  - Penetrative stunning (especially forcing air into cranial cavity) and "pithing" may embolize brain tissue.
  - Brain may leak from a cranial wound into collected blood.

Assurance of Bovine Materials Free of BSE Agent

- **Source cattle were reliably traceable to BSE-free countries.**

  If not, then the following precautions might have mitigated BSE risk:
- Animals were certifiably healthy:
  - Inspected and passed by national control authorities
  - From herds--preferably "closed"--with no history of BSE and under active surveillance for TSE
- Animals were never fed supplements containing ruminant meat-and-bone meal (documented).

Assurance that Bovine Materials are Free of BSE Agent (continued)

- Animals were young (e.g., per UK "over-thirty-months scheme"), hence unlikely to be in late incubation period of BSE.
- All bovine materials were derived only from minimal-risk tissues.
- Contamination of minimal-risk tissues with higher-risk tissues was avoided.
  - Animals were not slaughtered by stunning with intracranial injection of air , "pithing," other penetration of skull.
  - "Specified risk materials" [SRM] were removed at the point of slaughter.

BSE and Vaccines: Additional Considerations

- **Manufacturing process**
  - Dilution is expected to reduce risk per dose.
  - Partition of infectivity between liquid and solid components in cultures and fermentations is uncertain.
  - Some steps (filtration, chromatography) may separate infectivity from end product.
  - Potential inactivating steps (? validated)
  - Potential replication in cell cultures (unlikely except in "neuronal" cells not used as substrates)
- **End use**
  - Intramuscular route is more risky than oral route.

Vaccinated Children Pose Special Regulatory Concerns

- Maximum lifetime to incubate slow infections
- Usually healthy at the time of treatment
- Considered "vulnerable" (according to current principles of medical ethics)
  - Legally unable to give informed consent
  - Receiving nonvoluntary treatment (required for school)
  - Expected to contribute to group immunity
- Vulnerable persons are entitled to the highest level of fiduciary protection. In general, only minimal risks are acceptable for them.
- Parental confidence must be maintained if universal immunization of children is to be achieved.